Widespread mosaicism

Although the ability to generate induced pluripotent stem cells (iPSCs) from somatic cells has revolutionized the field of regenerative medicine, reports of genomic instability in stem and precursor cells suggest that these iPSCs may harbor copy-number variations (CNVs) in addition to single-base-pair changes. To examine this possibility, Abyzov and colleagues recently utilized next-generation sequencing to facilitate whole-genome and transcriptome analysis of 20 human iPSC lines generated from fibroblasts. On average, the iPSC lines contained two CNVs; interestingly, 50% of the CNVs were found as low-frequency somatic genomic variants in the original parental fibroblasts. Thus, these iPSC lines exhibited genomic stability, and the presence of the variants in the parental cells supports widespread somatic mosaicism for CNV in the genomes of the fibroblasts. On the assumption that each iPSC colony represents a single clone, the authors estimate that 30% of skin fibroblasts contain large somatic CNVs. If this estimate is validated, these findings will challenge the basis for genetic disease analysis. (*Nature* 492:438–42, 2012) *Selected by S. Yuspa*

Next-generation disease investigation

Technical advances in next-generation sequencing offer opportunities to identify gene mutations in unresolved cases of many diseases, including the inherited skin fragility disorders collectively termed epidermolysis bullosa. McGrath and colleagues recently employed whole-exome sequencing of three siblings with skin fragility to identify a homozygous 1-bp deletion (c.5786delC) in *EXPH5*, the gene that encodes the Rab27B GTPase effector protein Slac2-b. Sanger sequencing confirmed the presence and segregation of this mutation in the family. This frameshift mutation results in premature termination and truncation of the 1,989-amino-acid Slac2-b protein by 52 residues. Although RT-PCR demonstrated expression of *EXPH5* mRNA in affected subjects and controls, immunohistochemical staining revealed a complete absence of this protein in patient skin samples. Furthermore, keratin filaments were disrupted in both patient and Slac2-b knockdown keratinocytes, supporting a role for Slac2-b in maintaining keratinocyte integrity and thus in preventing skin fragility. These exciting findings expand the clinicopathological spectrum of epidermolysis bullosa and highlight the utility of whole-exome sequencing in unraveling disease etiology. (*Am J Hum Genet* 91:1115–21, 2012) *Selected by K. Green*

Cellular sprayground

Standard treatment with infection control, primary dressings, and high-strength compression results in healing of only 30–75% of venous leg ulcers. Kirsner and colleagues explored the effectiveness of a previously developed spray-applied cell therapy with cryopreserved human allogeneic, growth-arrested fibroblasts and keratinocytes from neonatal foreskin (HP802-247) for the treatment of venous leg ulcers in a phase II, multicenter, double-blind, randomized, placebo-controlled trial of 205 patients. Treatment resulted in enhanced wound closure, reduced healing time, and a larger proportion of closed wounds as compared with vehicle alone or with reported effects of standard treatments. The group that received 0.5×10^6 cells/ml every 14 days exhibited the best results, with minimal adverse events. These promising results highlight the need for larger randomized trials that directly compare this sprayed-cell technique with standard treatment for venous leg ulcers. (*Lancet* 380:977–85, 2012) *Selected by T. Nijsten*

Strategic location

Approximately 20 billion T cells reside in human skin, and nearly all of these are skin-homing memory T cells. Skin-resident Langerhans cells (LCs) are poised to interact with these memory T cells in the skin; however, the physiological role of LCs with respect to immunoregulation versus immunostimulation remains controversial. Seneschal and colleagues recently demonstrated that LCs induced $CD4^+CD25^+FoxP3^+CD127^-$ skin-resident regulatory T cells (Tregs) to proliferate. These memory Tregs were located within or near the epidermis or follicular epithelium—sites that are proximal to LCs. Importantly, pathogenic antigen exposure to *Candida albicans* resulted in LC induction of pathogen-specific effector memory T cells as well as Tregs. Thus, the biological context dictates the function of LCs in maintaining peripheral tolerance or activating protective skin-resident memory T cells to mount an effective host response. (*Immunity* 36:873–4, 2012) *Selected by S. Hwang*

Beyond antibody replacement

In a recent thought-provoking review, Erwin Gelfand described the use of intravenous immune globulin in autoimmune and inflammatory diseases. Despite the introduction of many new biologics to combat inflammation and autoimmunity, immune globulin treatment, which was developed in the 1950s, remains not only a lifesaving treatment for patients with antibody deficiency but also an important treatment for those with blistering skin disease, transplant rejection, neurologic disease, and other inflammatory and autoimmune diseases. Effects on various effector cell types, cytokines, chemokines, and other mediators have been ascribed to this agent, but it remains to be seen whether a single mechanism of action underlies the varied effects of intravenous immune globulin. Doses for autoimmune and inflammatory disease treatments are often four to five times greater than those used to treat immunodeficiency; thus, future studies to decipher the mechanism of action of this treatment in order to eventually replicate the specific effector are necessary to meet the demand for this biologic. (*N Engl J Med* 367:2015–25, 2012) *Selected by B. Gilchrest*

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